IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 18-651-CFC
TEVA PHARMACEUTICALS USA, INC., et al.	)	**CONSOLIDATED**
Defendants.	)	

DEFENDANTS' PROPOSED FINDINGS OF FACT

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PROPOSED FINDINGS OF FACT

Defendants Teva Pharmaceuticals USA, Inc., Apotex Inc., and Apotex Corp. hereby submit the following Post-Trial Proposed Findings of Fact based on the testimony of fact and expert witnesses and exhibits admitted at trial.

I. Witnesses

A. Defendants' Expert Witnesses

1. Dr. Jonathan Emens

1. Dr. Emens currently serves as the Deputy Director of Mental Health at the VA Portland Health Care System. Tr. 701:13-14 (Emens). He is an Associate Professor in the Department of Psychiatry and the Department of Medicine at Oregon Health and Science University. Tr. 701:14-19. He also works as a physician in the VA treating circadian rhythm sleep disorders, including Non-24. Tr. 701:18-19.

2. The parties do not dispute that Dr. Emens is an expert in the field of diagnosing and treating sleep disorders and the fields of circadian physiology, circadian rhythm sleep disorders, and Non-24 Hour Sleep Wake Disorder. Tr. 700:13-19; *see* D.I. 299 ¶ 1; DTX-397. Dr. Emens has over 30 years of experience researching circadian physiology and Non-24. Tr. 702:12-13. His experience in these fields first began before he entered medical school when he worked under Dr. Charles Czeisler at Brigham and Women's Hospital and Harvard Medical School. Tr. 702:12-15. Dr. Emens would later work with Drs. Alfred Lewy and

Robert Sack, who were the first to successfully demonstrate that melatonin could entrain individuals with Non-24. Tr. 702:16-19. Dr. Emens has since served on the American Academy of Sleep Medicine's task force for the treatment of circadian rhythm sleep disorders. Tr. 702:22-24. Dr. Emens continues to perform federally funded research on circadian physiology and circadian rhythm sleep disorders, including Non-24. Tr. 702:24-703:1.

3. At the close of Defendants' case-in-chief on invalidity, the Court found Dr. Emens to be a highly credible expert witness. Tr. 1257:25-1258:11.

2. Dr. David Greenblatt

4. The parties do not dispute that Dr. Greenblatt is an expert in the field of clinical pharmacology, which includes drug metabolism and drug interactions. Tr. 1028:5-10 (Greenblatt); D.I. 299 ¶ 1.

5. Dr. Greenblatt is currently a full-time professor at Tufts University School of Medicine. Tr. 1025:20-22; DTX-398.1-398.2. He received a bachelor's degree from Amherst College and his medical degree from Harvard University. Tr. 1026:10-17; DTX-398.1.

6. Dr. Greenblatt is the current editor-in-chief of the biomedical journal Clinical Pharmacology in Drug Development and served for forty years as the co-editor-in-chief of the Journal of Clinical Psychopharmacology. Tr. 1027:5-16; DTX-398.4. Dr. Greenblatt has also been a member of a number of scientific

societies, including serving as president of the American College of Clinical Pharmacology. Tr. 1027:17-19; DTX-398.4.

7. Dr. Greenblatt has published extensively in his field, with over 1,100 publications indexed on the National Library of Medicine, 780 of which are original research articles. Tr. 1027:20-23; DTX-398.4-398.99.

8. He has also received numerous awards over the course of his career, the most recent being the Oscar B. Hunter award in therapeutics, which is awarded to individuals for lifetime achievement in pharmacology and therapeutics. Tr. 1027:24-1028:4; DTX-398.2-398.3.

[Proposed findings of fact ¶¶ 9–16 were reserved for material related to claim 10 of U.S. Patent No. 10,829,465. Vanda has since has dismissed with prejudice its allegations that Defendants infringe that patent. *See* D.I. 310.]

II. The Asserted Method-of-Treatment Patents Are Invalid.

A. Level of Ordinary Skill

17. A person having ordinary skill in the art to which the RE604 patent and ’487 patent pertain would have at least 2-3 years of post-residency experience and/or training in the diagnosis and treatment of patients with sleep disorders and/or circadian rhythm disorders, and, in particular, education, training, and/or clinical experience in treating non-24. Tr. 705:9-22 (Emens); D.I. 308-5 at DDX-05.9.

18. For purposes of the ’829 and ’910 patents, the person of ordinary skill would also work as part of a team with, for example, individuals with training and experience in clinical pharmacology and drug development, such as Dr. Greenblatt. Tr. 705:9-22 (Emens); D.I. 308-5 at DDX-05.9; *see* Tr. 1028:5-10, 1029:5-12 (Greenblatt).

B. Scope and Content of the Prior Art

19. The RE604 patent is entitled to a priority date no earlier than January 26, 2012. D.I. 287, JPTO Ex. 1 at ¶ 40; JTX-1 (RE604 Patent).

20. The ’487 patent is entitled to a priority date no earlier than November 12, 2013. D.I. 287, JPTO Ex. 1 at ¶ 80; JTX-5 (’487 Patent).

21. The ’829 patent is entitled to a priority date no earlier than October 15, 2012. D.I. 287, JPTO Ex. 1 at ¶ 70; JTX-3 (’829 Patent).

22. The ’910 patent is entitled to a priority date no earlier than November 12, 2013. D.I. 287, JPTO Ex. 1 at ¶ 75; JTX-4 (’910 Patent).

1. As of January 26, 2012, skilled artisans knew that exogenous melatonin could effectively entrain blind people with Non-24.

23. A person of ordinary skill knew that the circadian rhythm is an endogenous (i.e., internal) biological clock in the human body located in the suprachiasmatic nucleus (“SCN”), a region of the human brain. Tr. 705:25-706:16 (Emens). A person of ordinary skill would understand that the circadian rhythm

acts as an internal pacemaker within the human body and follows a periodicity or timing of roughly 24 hours. *Id.* The circadian rhythm is responsible for regulating a wide variety of physiological and behavioral rhythms in humans, such as core body temperature and the natural production of hormones like cortisol and melatonin. *Id.* Relevant here, it was known in the prior art that the circadian rhythm controlled a person's internal desire for sleep. Tr. 706:10-16.

24. It was known in the prior art that a circadian rhythm sleep disorder ("CRSD") is the result of a mismatch between a person's circadian rhythm and the external 24-hour day. Tr. 706:17-21. As a result, that person feels the need to sleep at an abnormal time. Tr. 706:17-21, 707:14-19. A common example of a circadian rhythm sleep disorder known in the prior art is jet-lag. Tr. 706:22-707:1.

25. A person of ordinary skill would understand that Non-24 is another example of a circadian rhythm sleep disorder found predominantly in those who are totally blind. Tr. 706:22-707:1, 707:20-708:15 (Emens). By default, most sighted and totally blind people have circadian rhythms that do not precisely follow a periodicity of 24 hours. Tr. 705:23-706:16. This poses little problem for sighted people because their perception of light keeps their circadian rhythms aligned with the external 24-hour day/light cycle. Tr. 707:20-708:15. But, because totally blind people with Non-24 cannot perceive light, their circadian rhythms do not remain synchronized to the external 24-hour day/light cycle. Tr. 707:20-

708:12. Thus, if a totally blind person's circadian rhythm, for example, followed a periodicity of roughly 24.5 hours, that person's circadian rhythm will "drift" approximately 30 minutes later each day. *Id.* As a result, a blind person with Non-24 will feel the internal need for sleep at abnormal times. Tr. 707:2-708:12.

26. The prior art also referred to Non-24 as "free-running disorder." Tr. 708:13-15.

27. By January 2012, two options for treating circadian rhythm sleep disorders (including Non-24) existed in the prior art. Tr. 708:16-709:3 (Emens). A person suffering from a CRSD could either take a sedative-hypnotic to help that person fall asleep at a desired time or take an agent that would reset the timing of the person's circadian rhythm so that it followed a normal 24-hour sleep-wake schedule. Tr. 709:4-17. The second treatment option was known in the art as "entrain[ing]" a patient. Tr. 709:15-17.

28. It was well known as early as 2000 that exogenous melatonin was an example of a drug that could entrain blind patients with Non-24 to a normal 24-hour sleep-wake cycle. Tr. 709:18-22. Persons of ordinary skill, moreover, knew the mechanism by which exogenous melatonin achieved entrainment. Tr. 709:23-25. Exogenous melatonin is a melatonin agonist that binds to the melatonin 1 and melatonin 2 receptors, often referred to as the MT1 and MT2 receptors. Tr. 710:1-3. It was known in the art that exogenous melatonin's binding affinities for these

receptors was what gave the drug its ability to reset or "phase shift" a person's circadian rhythm and thereby entrain them to a normal 24-hour cycle. *Id.*

29. By 2007, the use of melatonin to treat Non-24 was formally recommended in the American Academy of Sleep Medicine's official practice parameters. DTX-37.11; *see* Tr. 722:20-723:22 (Emens). By that time, the prior art described the "[d]aily administration of exogenous melatonin [a]s the current treatment of choice for this so-called 'non-24 h sleep/wake disorder.'" DTX-39.1 (Skene & Arendt 2007).

2. As of January 26, 2012, skilled artisans knew that tasimelteon was a melatonin agonist with similar properties to exogenous melatonin.

30. Bristol Myers Squibb ("BMS") first formulated tasimelteon in 1999. JTX-12. By that year, BMS had also patented both the composition of tasimelteon and methods of using tasimelteon to treat circadian rhythm sleep disorders. JTX-12.24. Thus, as early as 1999, the prior art discussed the use of tasimelteon to treat circadian rhythm disorders.

31. Early animal studies of tasimelteon concluded that tasimelteon was "a novel melatonin receptor agonist that may be a useful treatment for sleep disorders that result from disruption of circadian rhythms" in humans. JTX-91.1 (Vachharajani 2003); Tr. 725:5-726:11 (Emens).

32. By 2007, Vanda filed an international patent application directed to administering tasimelteon to treat circadian rhythm disorders and sleep disorders. DTX-41 ("'244 Publication"). Vanda's application describes tasimelteon as a "specific and potent agonist of the MT1[] and MT2[] melatonin receptors" in the human brain and "demonstrat[ing] potent chronobiotic activity" in the human body. DTX-41.2; *see* Tr. 727:15-19 (Emens).

33. Other prior-art references concluded that (1) tasimelteon was like exogenous melatonin in that both had similar binding affinities for the MT1 and MT2 receptors and could phase-shift a person's circadian rhythm and (2) tasimelteon could therefore potentially entrain patients suffering from circadian rhythm sleep disorders. DTX-16.1 (Hardeland 2009) ("Tasimelteon . . . is a melatonin receptor agonist. Because of the high density of melatonin receptors in the circadian pacemaker, the suprachiasmatic nucleus, melatonergic actions can phase-shift circadian rhythms and promote sleep."); DTX-20.6 (Lankford 2011) ("[T]asimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin. Therefore, tasimelteon should be especially well suited for treatment of CRSDs [circadian rhythm sleep disorders] . . . Tasimelteon has already demonstrated its circadian phase-resetting effects.").

34. Vanda's CEO wrote in a 2009 article that "a phase-shifting drug, such as tasimelteon, has therapeutic potential for circadian rhythm sleep disorders." Tr. 175:7-10 (Polymeropoulos).

3. The prior art discloses administering tasimelteon as a once-daily oral dose of 20 milligrams 0.5 to 1.5 hours before bedtime.

35. A skilled artisan would know that Vanda sought international patent protection in 2007 for orally administering 20 milligrams of tasimelteon, once a day, 0.5 to 1.5 hours before bedtime. DTX-41.25-26; Tr. 727:23-728:6 (Emens).

36. By 2010, a person of ordinary skill in the art would also know from the prior art that Vanda had initiated a phase III clinical trial for tasimelteon in which totally blind subjects with Non-24 were being administered the drug in 20 milligram doses. DTX-20.6; Tr. 797:3-12, 799:8-15 (Emens).

4. The prior art discloses substantial information about tasimelteon's metabolism and potential drug-drug interactions.

37. A skilled artisan would have had extensive background knowledge concerning the need to avoid drug-drug interactions. For example, a skilled artisan would have known that the cytochrome P450 ("CYP450") family of enzymes plays an important role in drug metabolism, Tr. 1030:5-1031:6 (Greenblatt); Tr. 1147:17-24 (Parkinson); *see also* DTX-9; JTX-95, and that six to eight CYP enzymes are responsible for the metabolism of nearly 90% of all drugs. Tr.

1031:18-25 (Greenblatt); Tr. 1147:7-13, 1147:25-1148:5 (Parkinson); *see also* JTX-95.1; DTX-9.2. A skilled artisan would have also known that CYP3A4 is of particular importance because it is the only CYP enzyme located in both the intestine and the liver, and because it metabolizes up to 50% of drugs used in clinical practice, either partially or entirely. Tr. 1032:1-7, 1053:23-1054:5 (Greenblatt); Tr. 1146:12-1147:6 (Parkinson); DTX-9.1.

38. A skilled artisan also would have been aware of FDA's requirements for in vitro testing of all new drugs in order to identify the enzymes that contribute to drug metabolism, Tr. 1032:23-1033:3, 1033:14-22 (Greenblatt), which includes testing for metabolism by CYP1A2 and CYP3A4, Tr. 1148:6-11 (Parkinson).

39. FDA requires in vitro testing as a first step in determining the possibility of a drug-drug interaction ("DDI"). *See, e.g.*, Tr. 1033:14-22 (Greenblatt).

40. A skilled artisan would have known that DDIs can occur when two drugs (e.g., Drug X and Drug Y) are co-administered, and Drug X acts on CYP enzymes to increase or decrease the metabolism of Drug Y. Tr. 1041:3-10 (Greenblatt). On one hand, when Drug X inhibits the activity of CYP enzymes that metabolize Drug Y, this results in reduced Drug Y metabolism and increased plasma concentrations of Drug Y. Tr. 1041:3-15 (Greenblatt). Such drugs are known as "CYP inhibitors," and there were many known examples. Tr. at 1042:9-

23 (Greenblatt); *see also* DTX-24.2, DTX-9.5, JTX-95.3. Specifically, it was common knowledge that fluvoxamine was one of the, if not the, strongest known inhibitors of CYP1A2. Tr. 1043:3-9 (Greenblatt); Tr. 1149:3-7 (Parkinson).

41. On the other hand, when Drug X induces the expression of CYP enzymes that metabolize Drug Y, this results in increased Drug Y metabolism and decreased plasma concentrations of Drug Y. Tr. 1041:3-22 (Greenblatt). Such a drug is known as a "CYP inducer," and many inducers of CYP enzymes were known. Tr. 1042:9-23 (Greenblatt); *see also* DTX-24.3, DTX-9.4-5, JTX-95.3. It was common knowledge that rifampicin (i.e., rifampin) was the strongest known inducer of CYP3A4. Tr. 1043:10-17 (Greenblatt); Tr. 1148:18-22 (Parkinson). A skilled artisan would have been aware that for any new drug, possible DDIs can be predicted even before the drug reaches the clinical phase of development. Tr. 1149:8-1150:14 (Parkinson); *see also* DTX-9.7.

42. As a part of conducting pre-clinical testing on tasimelteon to identify possible DDIs, a skilled artisan would have been aware of the prior FDA approval of ramelteon, and that tasimelteon and ramelteon bind to the same melatonin receptors (i.e., MT1 and MT2) and have similar half lives in the body. Tr. 1035:7-18, 1037:5-18, 1040:6-19 (Greenblatt); *see also* DTX-16.3; JTX-035.1, 35.3. Further, a skilled artisan would have looked to ramelteon as relevant to understanding possible DDIs for tasimelteon because ramelteon and tasimelteon

are structurally similar, as both drugs have a dihydrobenzofuran structure and a propanamide residue. Tr. 1040:6-22 (Greenblatt); DTX-16.4-16.5. Finally, a skilled artisan would have known that ramelteon is metabolized by CYP1A2 and CYP3A4. Tr. 1038:25-1039:13, 1040:6-24 (Greenblatt); Tr. 1156:6-10 (Parkinson); *see also* JTX-93.4; JTX-35.2, 35.10.

43. A skilled artisan also would have known that ramelteon's in vivo metabolism resulted in very large DDIs with fluvoxamine (CYP1A2 inhibitor) and rifampin (CYP3A4 inducer). First, it was known that ramelteon underwent a 100-fold increase in blood plasma levels when it was co-administered with the CYP1A2 inhibitor fluvoxamine. Tr. 1043:18-1045:12, 1116:24-1117:13 (Greenblatt); *see also* DTX-28.9; JTX-93.4. A skilled artisan would have known that any DDI resulting in a 5-fold change in blood plasma levels is considered "large" by FDA standards, and therefore a skilled artisan would have viewed the ramelteon-fluvoxamine DDI as a "huge interaction" and clearly significant. Tr. 1045:15-23 (Greenblatt).

44. Second, it was known that ramelteon underwent an 80% decrease in blood plasma levels when it was co-administered with the CYP3A4 inducer rifampin. Tr. 1046:5-21 (Greenblatt); *see also* JTX-35.10. Further, a skilled artisan would have been aware that these well-known DDIs for ramelteon are reflected in its FDA-approved label, which discloses that ramelteon and fluvoxamine should

not be co-administered, Tr. 1045:24-1046:3, 1116:24-1117:13 (Greenblatt); JTX-35.8, 35.10; JTX-93.4, and that ramelteon co-administration with rifampin results in decreased exposure and efficacy may be reduced, Tr. 1046:5-1047:5 (Greenblatt); *id*. 1116:24-1117:13 (Greenblatt); *see also* JTX-35.10, JTX-93.4.

C. Claim 3 of the RE604 Patent is invalid as obvious in light of the prior art.

45. Asserted claim 3 of the RE604 patent depends from claim 2, which depends from claim 1. Claim 1 recites "[a] method of entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours, and maintaining said 24 hour sleep-wake cycle comprising: treating the patient by orally administering to the patient 20 mg of tasimelteon once daily before a target bedtime." JTX-1.41 (38:25-31). Claim 2 specifies that the "patient is totally blind." *Id.* (38:32-33). Claim 3 specifies that "the tasimelteon is administered 0.5 to 1.5 hours before the target bedtime." *Id.* (38:34-35).

1. The combination of Lankford, Hack, and the '244 Publication or Hardeland, Hack, and the '244 Publication renders claim 3 of the RE604 patent invalid as obvious.

(a) The Prior Art

(i) Hack

46. Hack, L., et al., "The Effects of Low-Dose 0.5-mg Melatonin on the Free-Running Circadian Rhythms of Blind Subjects," ("Hack") was published in

2003 and therefore qualifies as prior art to the RE604 patent. JTX-146; Tr. 718:24-719:15 (Emens). It is a research paper studying the use of low-dose exogenous melatonin to entrain blind individuals with Non-24. *Id.* 719:16-20.

47. Hack explains that "[t]he aim of developing melatonin treatment regimens to entrain the underlying circadian oscillator is to optimally treat the clinical 'non-24-h sleep-wake disorder' condition that develops as a result of misalignment of the circadian system with the social 24-h day." JTX-146.8.

48. Hack states that "several recent studies have reexamined the ability of melatonin to entrain free-running rhythms in totally blind people and found that entrainment could be achieved following daily oral melatonin treatment" with doses including 5, 10, and 0.5 milligrams of melatonin. JTX-146.2.

49. Hack states that "[p]revious studies have shown that chronic usage of melatonin is necessary for free-running blind people to remain entrained to the 24-h day." *Id.*

50. Hack's study concludes "that a daily dose of 0.5 mg melatonin is effective at entraining the free-running circadian systems in most of the blind subjects studied" and that "[o]ptimal treatment with melatonin for this non-24-h sleep disorder should correct the underlying circadian disorder (to entrain the sleep-wake cycle)." JTX-146.1.

(ii) Lankford

51. Lankford, D., "Tasimelteon for insomnia" ("Lankford") was published in 2011 and therefore qualifies as prior art to the RE604 patent. DTX-20; Tr. 798:11-14 (Emens). Lankford is a review article disclosing the use of tasimelteon to treat insomnia. Tr. 798:24-799:2 (Emens).

52. Lankford discloses that "tasimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin" and has "already demonstrated its circadian phase-resetting effects" in the clinical trial setting. DTX-20.6. It concludes that tasimelteon should therefore "be especially well suited for treatment of" circadian rhythm sleep disorders. *Id.*

53. Lankford also discloses several clinical studies in which 20 and 50 milligram doses of tasimelteon were administered to healthy volunteers and patients with insomnia 30 minutes before bedtime. DTX-20.4, 20.5.

54. Lankford also states that there is "an ongoing Phase III trial of tasimelteon in blind people with no light perception and with non-24 h[our] sleep-wake disorder" that is "designed to assess the effectiveness of 20 mg [of] tasimelteon." DTX-20.6. The clinical trial to which Lankford was referring was Vanda's clinical trial for Hetlioz. Tr. 799:8-15 (Emens).

(iii) Hardeland

55. Hardeland, R., "Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders" ("Hardeland") was published in 2009 and therefore qualifies as prior art to the RE604 patent. DTX-16; Tr. 729:21-730:2 (Emens).

56. Hardeland states that "[t]he chronobiotic effects of melatonin are predominantly exerted through its binding to the G-protein-coupled melatonin receptors" which are "located in the suprachiasmatic nucleus (SCN), which acts as the circadian pacemaker." DTX-16.1. Hardeland discloses that "[m]elatonin has been used to treat various circadian and sleep disorders" and states that "[s]uch treatments are particularly successful if the primary objective is to readjust the circadian phase." DTX-16.2.

57. Hardeland describes tasimelteon as "a melatonin receptor agonist" and "an investigational melatonergic drug" that is "being developed for the treatment of insomnia, circadian rhythm sleep disorders and depression." DTX-16.1, 16.2. Hardeland observes that "current knowledge indicates that tasimelteon is suitable for phase-shifting the circadian clock." DTX-16.8.

58. Hardeland states that tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders" or "other types of

entrainment difficulties" and observes that "[t]hese properties are expected from a melatonergic drug" and have "also [been] observed with melatonin." DTX-16.7.

(iv) '244 Publication

59. International Patent Application Number WO 2007/137244 ("'244 Publication") was filed by Vanda on May 22, 2006, and it was published on November 29, 2007 and therefore qualifies as prior art to the RE604 patent. DTX-41; Tr. 726:12-727:8 (Emens). The '244 Publication is directed to "a method of administering MA-1 to a human subject in need thereof which comprises orally administering MA-1 to the subject in an amount of about 10 mg to about 100 mg per day." DTX-41.3. The '244 Publication further describes the inventive subject matter pertaining to the "use of the melatonin agonist herein referred to as MA-1, to treat sleep disorders and circadian rhythm disorders." *Id.*

60. MA-1 is tasimelteon. Tr. 727:13-14 (Emens).

61. The '244 Publication discloses that "MA-1 is a specific and potent agonist of the MT1R and MT2R melatonin receptors in the Suprachiasmatic nucleus (SCN), the region of the brain associated with the biological clock. Engagement of these receptors by melatonin is believed to regulate circadian rhythms, including the sleep/wake cycle. Consistent with its receptor binding profile, MA-1 demonstrates potent chronobiotic activity in preclinical models of acute phase-shifting and chronic re-entrainment." DTX-41.2.

62. The ’244 Publication describes several clinical studies assessing the safety and efficacy of tasimelteon and concludes from these studies that tasimelteon “was well-tolerated at doses of 10, 20, 50, and 100 mg.” DTX-41.23.

63. The ’244 Publication concludes further that “[a]n oral dose of about 20 to about 50 mg [of tasimelteon] is effective in treating sleep disorders when administered about 1/2 hour before sleep time.” DTX-41.24.

64. The ’244 Publication explains that treatment with tasimelteon “is continued until the patient’s circadian rhythm is restored to normal, i.e., until the patient’s normal daily function is not inhibited by the underlying circadian rhythm disorder.” DTX-41.5, 41.6. It goes on to state that treatment with tasimelteon “can continue for some time after these end points are achieved so as to lessen the likelihood of relapse.” DTX-41.6.

65. Claim 5 of the ’244 Publication claims administering tasimelteon “to treat or prevent a circadian rhythm disorder or a sleep disorder.” DTX-41.25.

66. Claim 8 of the ’244 Publication depends from claim 7 and specifies that the tasimelteon is “administered at about 0.5 hours prior to bedtime.” *Id.*

67. Claim 9 of the ’244 Publication depends from claim 8 and specifies that the tasimelteon “is orally administered at a dose of about 20 mg/day or about 50 mg/day.” DTX-41.26.

(b) The combinations of Lankford, Hack, and the '244 Publication and Hardeland, Hack, and the '244 Publication teach or suggest every claim element of the RE604 patent.

(i) A method of entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours

68. Lankford, Hardeland, Hack, and the '244 Publication each teach or suggest "entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours." Tr. 803:8-16; 811:24-812:1 (Emens).

69. Hack explicitly discloses a study in which blind patients with Non-24 were successfully entrained to 24-hour sleep-wake cycles with exogenous melatonin. JTX-146.1; Tr. 804:8-20 (Emens). It discloses further that these patients slept an average of 6.6 hours per night, with a standard deviation of 1.1 hours. JTX-146.6; Tr. 804:21-805:5 (Emens). A person of ordinary skill in the art would therefore construe Hack as teaching or suggesting entraining a patient with Non-24 to a 24 hour sleep-wake cycle where the patient sleeps for approximately 7 to 9 hours. Tr. 803:8-16.

70. Lankford observes that "tasimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin" and "has already demonstrated its circadian phase-resetting effects." DTX-20.6. It concludes

that "[t]asimelteon should be especially well suited for the treatment of CRSDs." *Id.* Because a person of ordinary skill in the art would understand that Non-24 was a type of circadian rhythm disorder and that one way of "treating" a circadian rhythm disorder was entraining the patient with a melatonin agonist with phase shifting, a person of ordinary skill in the art would understand Lankford as teaching or suggesting that tasimelteon could likely entrain blind patients with Non-24. Tr. 803:17-804:7 (Emens).

71. Lankford further discloses a Phase III clinical trial in which blind patients with Non-24 were being administered tasimelteon. DTX-20.6; Tr. 803:17-21 (Emens). This would also suggest to a person of ordinary skill that tasimelteon could entrain blind patients with Non-24. Tr. 803:17-804:7 (Emens).

72. Hardeland notes that tasimelteon "is a melatonin receptor agonist" and explains that "melatonergic actions can phase-shift circadian rhythms and promote sleep." DTX-16.1. It states further that tasimelteon has proven effective "in resetting the circadian rhythm . . . which indicate[s] its potential suitability as treatment for . . . circadian rhythm sleep disorders." *Id.* A person of ordinary skill in the art would therefore understand Hardeland to teach or suggest that tasimelteon can entrain blind patients with Non-24. Tr. 811:24-812:12 (Emens).

73. The '244 Publication states that tasimelteon is a "specific and potent agonist" of the MT1 and MT2 receptors and that "[e]ngagement of these receptors

by melatonin is believed to regulate circadian rhythms, including the sleep/wake cycle." DTX-41.2. It states further that tasimelteon "demonstrates potent chronobiotic activity in preclinical models of acute phase-shifting and chronic re-entrainment." *Id.* A person of ordinary skill in the art would understand the '244 Publication as teaching or suggesting the concept of entraining patients with circadian rhythm sleep disorders, including Non-24. Tr. 805:6-17 (Emens).

(ii) and maintaining said 24 hour sleep-wake cycle

74. Hack and the '244 Publication both teach or suggest the "maintaining said 24 hour sleep-wake cycle" limitation. Tr. 805:18-23 (Emens).

75. Hack states that "[p]revious studies have shown that chronic usage of melatonin is necessary for free-running blind people to remain entrained to the 24-h day." JTX-146.2. A person of ordinary skill in the art would interpret this language in Hack as teaching or suggesting that once a patient with Non-24 is entrained to a 24 hour sleep-wake cycle, that patient must continue receiving tasimelteon to maintain a 24 hour sleep-wake cycle—i.e., that patient must continue taking tasimelteon to maintain entrainment. Tr. 805:24-806:4 (Emens).

76. The '244 Publication states that treatment with tasimelteon "is continued until the patient's circadian rhythm is restored to normal" and discloses further that "[t]reatment can continue for some time after these end points are achieved so as to lessen the likelihood of relapse." DTX-41.5-6. A person of

ordinary skill in the art would interpret this language as synonymous with the concept of post-entrainment "maintaining" of a person's 24 hour sleep-wake cycle. Tr. 806:5-11 (Emens).

(iii) treating the patient by orally administering to the patient 20 mg of tasimelteon

77. Lankford, Hardeland, and the '244 Publication each teach or suggest "treating the patient by orally administering to the patient 20 mg of tasimelteon." Tr. 806:12-15, 812:13-23 (Emens).

78. The '244 Publication explicitly claims administering tasimelteon in the claimed oral dosage amount of 20 milligrams. Claim 1 of the '244 Publication discloses orally administering tasimelteon to a patient "in an amount of about 10 mg to about 100 mg per day." DTX-41.25. Claim 4 of the '244 Publication depends from claim 1 and specifies a dose range of "about 20 mg to about 50 mg." *Id.* Claim 5 of the '244 Publication depends from claim 4 and specifies that the tasimelteon is being administered "to treat or prevent a circadian rhythm disorder or sleep disorder." *Id.* The '244 Publication elsewhere discloses that "[a]n oral dose of about 20 to about 50 mg" of tasimelteon "is effective in treating sleep disorders." DTX-41.24. A person of ordinary skill in the art would therefore construe the '244 Publication as teaching or suggesting orally administering 20 milligrams of tasimelteon to a patient, once a day, to treat or prevent a circadian rhythm sleep disorder such as Non-24. Tr. 806:23-807:12 (Emens).

79. Lankford discloses that "[t]here is an ongoing Phase III trial of tasimelteon in blind people with no light perception and with Non-24 h sleep-wake disorder. The trial is designed to assess the effectiveness of 20 mg tasimelteon." DTX-20.6. Thus, a person of ordinary skill in the art would understand that Lankford is teaching or suggesting administering 20 milligrams of tasimelteon to a totally blind patient with Non-24. Tr. 806:16-22 (Emens).

80. Hardeland discloses several clinical trials where healthy volunteers and subjects with insomnia received tasimelteon in dose ranges that included 20 milligrams. DTX-16.5-6. Hardeland states further that "[t]he most effective doses of tasimelteon were in the range of 20 to 50 mg/day." *Id.* at 7. A person of ordinary skill in the art would therefore interpret Hardeland as teaching or suggesting orally administering 20 milligrams of tasimelteon. Tr. 812:13-23 (Emens).

(iv) once daily before a target bedtime

81. Lankford, Hardeland, and the '244 Publication each teach or suggest administering tasimelteon "once daily before a target bedtime." Tr. 807:13-23, 812:24-813:9 (Emens).

82. The '244 Publication explicitly claims administering the tasimelteon within the time schedule of once a day before a target bedtime. Claim 8 discloses administering tasimelteon "at about 0.5 hours prior to bedtime," while claim 9, which depends from claim 8, specifies that the tasimelteon "is orally administered

at a dose of about 20 mg/day." The '244 Publication states further that "[s]ince peak plasma concentration (C_{max}) is reached at 0.5-1 hour after oral administration[], MA-1 was administered 30 minutes prior to bedtime." DTX-41.11. Thus, a person of ordinary skill in the art would take the '244 Publication as teaching or suggesting orally administering 20 milligrams of tasimelteon once a day before bedtime. Tr. 808:10-20 (Emens).

83. Lankford discloses several clinical trials where tasimelteon was administered to healthy volunteers and patients with insomnia. DTX-20.5. Lankford explains that, in each of these trials, subjects were administered tasimelteon 30 minutes before bedtime. *Id.* A person of ordinary skill in the art would therefore recognize that Lankford teaches administering tasimelteon before a target bedtime. Tr. 807:24-808:9 (Emens).

84. Hardeland describes several clinical trials where healthy volunteers and subjects with insomnia received 20 milligrams of tasimelteon "30 min before bedtime." DTX-16.5-6. Hardeland also explains that in at least one of these studies the participants received the tasimelteon doses for three consecutive days. *Id.* at 5. A person of ordinary skill in the art would thus read Hardeland as teaching or suggesting administering tasimelteon once daily before a target bedtime. Tr. 812:24-813:9 (Emens).

(v) wherein the patient is totally blind

85. Lankford and Hack each disclose the RE604 patent's limitation requiring that the patient "is totally blind." Tr. 808:21-809:1 (Emens).

86. Lankford discloses Vanda's Phase III clinical trial for tasimelteon and states that the patients in that trial were blind "with no light perception and with non-24 h[our] sleep-wake disorder." DTX-20.6; Tr. 809:2-9 (Emens). A skilled artisan would know that a blind person without light perception is a totally blind person. *Id.* Lankford therefore teaches or suggests administering tasimelteon to a totally blind patient with Non-24. *Id.*

87. Hack discloses a study assessing the entraining ability of exogenous melatonin and discloses that the patients in that study were totally blind and had Non-24. JTX-146.1; Tr. 809:10-16 (Emens). Hack therefore teaches or suggests using a melatonin agonist, such as tasimelteon, to entrain blind patients with Non-24. *Id.*

(vi) wherein the tasimelteon is administered 0.5 to 1.5 hours before the target bedtime.

88. Lankford, the '244 Publication, and Hardeland each teach or suggest the RE604 patent's limitation requiring administering the tasimelteon "0.5 to 1.5 hours before the target bedtime" for the same reasons provided above with respect to the "once daily before a target bedtime" limitation.

(c) A skilled artisan would have had a motivation to combine Lankford, Hack, and the ’244 Publication or Hardeland, Hack, and the ’244 Publication and would have had a reasonable expectation of success of thereby arriving at the claimed invention.

89. A skilled artisan would have had an apparent reason to combine the Lankford or Hardeland references with the Hack and ’244 Publication references and would have had a reasonable expectation of success in entraining a totally blind patient with Non-24 to a 24 hour sleep-wake cycle. Tr. 809:17-811:16, 813:10-815:3 (Emens). Hack would teach a skilled artisan that exogenous melatonin can entrain blind patients with Non-24. Tr. 810:4-7 (Emens). A skilled artisan would have understood from Lankford, Hardeland, and the ’244 Publication that tasimelteon binds to the same MT1 and MT2 receptors as exogenous melatonin and can also cause phase shifts and therefore entrainment. Tr. 810:8-14, 813:19-814:3 (Emens). A skilled artisan would further understand from Lankford, Hardeland, and the ’244 Publication that tasimelteon would likely be an effective treatment for circadian rhythm sleep disorders, which would include Non-24. Tr. 810:15-19 (Emens).

90. Lankford’s disclosure of an ongoing Phase III clinical trial in which researchers were assessing the efficacy of 20 milligrams of tasimelteon in blind patients with Non-24 would likewise have motivated a skilled artisan to combine these references to arrive at the claimed invention. Tr. 811:6-16 (Emens). A skilled

artisan would understand that advanced clinical testing, such as a Phase III clinical trial, requires a substantial amount of time and money to organize and perform. *Id.* A skilled artisan would therefore recognize that drug sponsors typically do not initiate Phase III clinical trials assessing the efficacy of a drug in treating a particular disease or disorder unless there is a reasonable expectation that the drug will prove effective in treating that disease or disorder. *Id.* Thus, the fact that a clinical trial assessing tasimelteon's ability to treat blind patients with Non-24 was already underway would motivate a person of ordinary skill in the art to practice the asserted claim of the RE604 patent. *Id.*

2. There are no secondary considerations that alter the conclusion that Claim 3 of the RE604 patent is invalid as obvious.

91. The only evidence Vanda presented at trial pertaining to secondary considerations was Dr. Charles Czeisler's testimony that the RE604 patent met "a long felt but previously unmet medical need" for treating totally blind patients with Non-24. Tr. 1186:3-1187:24 (Czeisler).

92. Dr. Czeisler's conclusory testimony on this score is not probative of non-obviousness. There was no long-felt need before January 2012 for a drug that could effectively treat blind patients with Non-24 because exogenous melatonin was well-established as effective at entraining, and therefore treating, blind patients with Non-24. Tr. 1217:7-13 (Emens).

93. Before January 2012, the available clinical data conclusively established that exogenous melatonin could effectively entrain and therefore treat totally blind people with Non-24. Tr. 1217:15-18, 1217:25-1218:21 (Emens). Furthermore, by January 2012, researchers and clinicians had made great strides in pinpointing the optimal dose and timeframe for administering tasimelteon to totally blind patients with Non-24. Tr. 1218:13-21. The more conservative estimates gauging the success rate of exogenous melatonin at entraining concluded that the compound could successfully entrain approximately two-thirds of blind patients with Non-24. Tr. 1217:25-1218:13. The general consensus as to exogenous melatonin's treatment efficacy had become so well-established before January 2012 that the American Academy of Sleep Medicine issued two sets of practice parameters recommending exogenous melatonin as the treatment option for Non-24. Tr. 1217:19-24.

94. Today, exogenous melatonin remains the preferred drug for treating blind patients with Non-24. For instance, the VA healthcare system, which is the "largest fully integrated healthcare system" in the United States, indicates exogenous melatonin for the treatment of Non-24 in its formulary. Tr. 1219:16-1220:15 (Emens). There is no such indication for tasimelteon. Tr. 1220:2-6.

D. Claim 3 of the RE604 patent is invalid as anticipated by Clinical Trials.[1]

1. Clinical Trials was publicly accessible on clinicaltrials.gov before the priority date of the RE604 patent.

95. Clinicaltrials.gov is a government website operated by the U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/home. Entities are required by law to submit to clinicaltrials.gov the protocols and results of clinical studies they sponsor. https://clinicaltrials.gov/ct2/manage-recs/background. The website contains a "History of Changes" feature, which offers users the option to see the date a sponsor submitted a given to protocol to the website as well as the contents of that protocol. Tr. 784:3-17, 786:11-17 (Emens).

96. According to this "History of Changes" feature on clinicaltrials.gov, Vanda first submitted the protocol for its Hetlioz Phase III clinical trial ("Clinical Trials") on July 13, 2010. Tr. 786:24-787:12, 790:17-24 (Emens). It further indicates that Clinical Trials was "first posted" on clinicaltrials.gov on July 15, 2010. Tr. 791:6-12. Defendants introduced into evidence a copy of that protocol, found at DTX-42.9-12, which is identical in substance to the version of the protocol available on clinicaltrials.gov. Tr. 790:25-793:8.

[1] Defendants propose the following findings of fact in the event the Court accepts Vanda's theory of induced infringement of the RE604 patent. *See* Defs.' Opening Post-Tr. Br. § I.B.2.

97. As of approximately July 15, 2010, Clinical Trials was available to the general public on clinicaltrials.gov. *Id.*; DTX-42.9-12. A person of ordinary skill in the art as of that time could have located Clinical Trials after having exercised reasonable diligence. Tr. 782:23-783:24 (Emens). Accordingly, Clinical Trials qualifies as prior art to the RE604 patent.

2. Clinical Trials discloses each of the claim elements of the RE604 patent that pertain to the RE604 patent's claimed patient group and dosage regimen.

(a) A patient suffering from Non-24

98. Clinical Trials is titled "Efficacy and Safety of Tasimelteon Compared with Placebo in Totally Blind Subjects with Non-24-Hour Sleep-Wake Disorder." DTX-42.9. Clinical Trials therefore discloses the limitation of administering tasimelteon to "a patient suffering from Non-24." *Id.*; Tr. 816:4-12 (Emens).

(b) Wherein the patient is totally blind

99. For the same reasons discussed in the preceding paragraph, Clinical Trials discloses the limitation of the RE604 patent that requires administering tasimelteon to a patient who "is totally blind." DTX-42.9; Tr. 817:6-10 (Emens).

(c) Orally administering to the patient 20 mg of tasimelteon

100. The "Arms" and "Assigned Interventions" sections of Clinical Trials each indicate administering tasimelteon to patients as "20 mg tasimelteon

capsules." DTX-42.10. Clinical Trials therefore discloses "orally administering to the patient 20 mg of tasimelteon." Tr. 816:13-21 (Emens).

(d) Once daily before a target bedtime

101. The "Study Description" section of Clinical Trials states that "subjects will be asked to take either tasimelteon or placebo approximately 1 hour prior to their target bedtime." DTX-42.9-10. Clinical Trials thus discloses administering tasimelteon "once daily before a target bedtime." Tr. 816:22-817:5 (Emens).

(e) Wherein the tasimelteon is administered 0.5 to 1.5 hours before the target bedtime.

102. For the same reasons discussed in the preceding paragraph, Clinical Trials discloses the RE604 patent's limitation of administering tasimelteon "0.5 to 1.5 hours before the target bedtime." DTX-42.9-10; Tr. 816:22-817:5 (Emens).

3. Clinical Trials discloses steps that inevitably result in "entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours" and "maintaining said 24 hour sleep-wake cycle."

103. Clinical Trials discloses the same administration steps as Vanda's and Defendants' labels. Tr. 817:16-818:19 (Emens); *compare* DTX-42.9-10, *with* JTX-28.1, 12 (tasimelteon drug label). Under Vanda's infringement theory, following the administration steps in Vanda's and Defendants' labels will inevitably lead to at least some physicians practicing the "entraining" and "maintaining" limitations of the RE604 patent. *See, e.g.*, Tr. 1224:13-16 (Vanda's counsel stating that "in our

view . . . you can't treat Non-24 with tasimelteon without being covered by" the RE604 patent). Accordingly, if that theory is accepted, following the administration steps disclosed by Clinical Trials will likewise inevitably lead to practicing the claims. Tr. 817:13-818:6 (Emens).

E. Claim 5 of the '487 patent is invalid as obvious.

104. Asserted claim 5 of the '487 patent depends from claim 4, which depends from claim 1. Claim 1 recites "[a] method of treating a human patient suffering from a circadian rhythm disorder or a sleep disorder that comprises orally administering to the patient an effective dose of tasimelteon without food, wherein the effective dose is 20 mg/d." JTX-5.4 (4:2-6). Claim 4 specifies that "the patient is suffering from a circadian rhythm disorder," and claim 5 further specifies that "the circadian rhythm disorder is Non-24 Disorder." *Id.* (4:13-16). The Court has construed "without food" to mean "the patient has not consumed food within 30 minutes prior to administration of tasimelteon and does not consume food with the administration of tasimelteon." D.I. 183 at 3.

105. The limitations of claim 5 that require administering 20 mg tasimelteon to treat Non-24 would have been obvious to a skilled artisan for the reasons discussed above with respect to claim 3 of the RE604 patent.

106. The additional limitation of claim 5 requiring that administration of tasimelteon be "without food" would likewise have been obvious in light of the

prior-art combinations of (i) Lankford, Hack, and the '244 Publication and (ii) Hardeland, Hack, and the '244 Publication. Each combination discloses administering tasimelteon 30 minutes before bedtime. Tr. 823:11-18 (Emens); *see* DTX-16.6 (Hardeland) (describing insomnia trials in which patients received tasimelteon 30 minutes before target bedtime); DTX-20.5 (Lankford) (same); DTX-41.10 ('244 Publication) (same); DTX-41.24 ('244 Publication) ("An oral dose of about 20 to about 50 mg is effective in treating sleep disorders when administered about 1/2 hour before sleep time."); DTX-41.25 ('244 Publication) (claiming a method of administering tasimelteon "at about 0.5 hours prior to bedtime"). Since most people do not eat right before they go to bed, a patient taking a drug 30 minutes before bedtime would "more likely than not" be taking the drug "without food" under the Court's claim construction. Tr. 823:14-18 (Emens).

107. Moreover, the prior art presented a binary choice—administer tasimelteon with food or without food. Tr. 823:19-23 (Emens). Accordingly, both options would have been obvious to a skilled artisan. *Id.*

F. Claim 5 of the '487 patent is invalid for lack of written description to the extent the Court finds that it requires improved efficacy in treating Non-24 when tasimelteon is administered without food.

108. Claim 5 recites a method of treating Non-24 by administering 20 mg/d tasimelteon without food. JTX-5.4 (4:2-6, 13-16). Claim 5 does not require that

administering tasimelteon without food is better at treating Non-24 than administering it with food. Tr. 824:20-24 (Emens). Nonetheless, Vanda asserts that it invented a method of administering tasimelteon without food that is more effective at treating Non-24 than if tasimelteon were administered with food. Tr. 825:5-12 (Emens).[2]

109. Even if '487 patent claimed a method of treating Non-24 by administering tasimelteon without food that was more effective than administering tasimelteon with food, the claims would be invalid for lack of written description because there is no data in the '487 patent to support Vanda's assertion. Tr. 825:13-826:1 (Emens); *see also* JTX-5. Indeed, the '487 patent only discloses the effects of administering tasimelteon to *sighted healthy individuals* with or without food. Tr. 826:14-18 (Emens); *see also* JTX-5. The results of that study provide information about how the pharmacokinetics of tasimelteon are affected by food, but they provide no information about whether administration with or without food is *better at treating Non-24. See* Tr. 827:19-828:3 (Emens). Moreover, in the food-

[2] Defendants understand Vanda to be arguing that the '487 patent claims incorporate a notion of increased efficacy in treating Non-24 when tasimelteon is administered without food as opposed to with food. If that is Vanda's argument, and if the Court agrees, the claim is invalid for lack of written description for the reasons explained in the text. If Vanda's argument is instead that the invention claimed in the '487 patent produced *unexpected results*, that argument is simply wrong because, as explained in the text, there is no evidence that administering tasimelteon without food is *better at treating Non-24* than administering it with food.

effect study described in the ’487 patent specification 100 mg tasimelteon was administered in the morning (at 6:00 AM), *see* JTX-5, so the results are particularly uninformative regarding the treatment of Non-24 by administering *20 mg* of the drug *before bedtime*.

110. Further, while the ’487 patent incorporates the patent application publication corresponding the RE604 patent, the RE604 patent likewise does not include studies that evaluate the effect of administering tasimelteon with and without food to Non-24 patients. Tr. 826:20-827:18 (Emens); *see also* JTX-5.3; JTX-1. As Defendants’ expert Dr. Emens explained, without a head-to-head trial where tasimelteon is administered with food to a group of patients with Non-24 and without food to a group of patients with Non-24, it is not possible to demonstrate that tasimelteon is more effective at treating Non-24 when administered without food versus with food. Tr. 827:19-828:3 (Emens). Accordingly, claim 5 of the ’487 patent is invalid for lack of written description if it requires improved efficacy in treating Non-24 with tasimelteon without food versus treating Non-24 with tasimelteon with food. Tr. 825:13-21 (Emens).

G. Claim 14 of the ’829 patent is invalid as obvious.

111. Asserted claim 14 of the ’829 patent depends from claim 13. Claim 13 recites “[a] method of treating a patient for a circadian rhythm disorder or for a sleep disorder wherein the patient is being treated with a strong CYP1A2 inhibitor

selected from a group consisting of fluvoxamine, ciprofloxacin, and verapamil, the method comprising: (A) discontinuing treatment with the strong CYP1A2 inhibitor and then (B) treating the patient with 20 mg of tasimelteon once daily." JTX-3.35 (38:52-60). Claim 14 specifies that the patient is being treated "for Non-24-Hour Sleep-Wake Disorder." *Id.* (38:61-62).

1. The combination of Lankford, Hack, the '244 Publication, and Hardeland or Hardeland, Hack, and the '244 Publication renders claim 14 of the '829 patent invalid as obvious.

(a) The Prior Art

(i) Hack, Lankford, and the '244 Publication

112. The teachings of Hack, Lankford, and the '244 Publication are discussed above in Sections II.C.1(a)(i), (ii), and (iv), respectively.

(ii) Hardeland

113. The teachings of Hardeland relevant to the method-of-treatment limitations are discussed above in Section II.C.1(a)(iii). In addition to those teachings, Hardeland also discloses that both tasimelteon and ramelteon bind to the MT1 and MT2 receptors with high affinity. DTX-16.2. Hardeland further discloses that tasimelteon and ramelteon have structural similarity, *i.e.,* are structural analogs, as both compounds share the dihydrobenzofuran structure and the propanamide residue. DTX-16.3-16.4.

114. Hardeland teaches that a study using microsomes that overexpress CYP isoenzymes "suggested that tasimelteon was primarily metabolized by the CYP1A2 . . . isoenzyme[.]" DTX-16.4 (citing Vachharajani (JTX-91)). Hardeland also teaches that because "tasimelteon is metabolized by the CYP isoenzymes 1A2 . . . coadministration of any drug that inhibits one of these isoenzymes should be regarded with caution." DTX-16.6.

(b) The combinations of Lankford, Hack, the '244 Publication, and Hardeland and Hardeland, Hack, and the '244 Publication teach or suggest every element of claim 14 of the '829 patent.

115. As explained above, treating Non-24 by administering 20 mg tasimelteon would have been obvious in view of Lankford, Hack, and the '244 Publication, as well as Hardeland, Hack, and the '244 Publication. And, for the reasons explained herein, the additional limitation added by claim 14—the requirement that administration of a strong CYP1A2 inhibitor be discontinued before starting tasimelteon—would have been obvious in view of Hardeland and the background knowledge of a skilled artisan. Tr. 1049:3-1050:19 (Greenblatt).

116. Hardeland discloses that tasimelteon is primarily metabolized by CYP1A2. Tr. 1036:3-16, 1049:3-25, 1100:2-9 (Greenblatt); *see also* DTX-16.4 (citing JTX-91.10). In view of this, Hardeland cautions against the administration of tasimelteon with CYP1A2 inhibitors. Tr. 1049:3-1050:9, 1067:17-20, 1069:7-22 (Greenblatt); *see also* DTX-16.6.

117. A skilled artisan intending to administer tasimelteon to a subject already taking a CYP1A2 inhibitor would have heeded this warning in Hardeland, particularly given the background knowledge of the very large DDI between ramelteon and fluvoxamine. Tr. 1043:18-1046:4, 1116:24-1117:13 (Greenblatt); *see also* DTX-28.9; JTX-93.4; JTX-35.10. Accordingly, a skilled artisan would have found it obvious over Hardeland in view of the background knowledge in the art to discontinue treatment with a strong CYP1A2 inhibitor such as fluvoxamine prior to treating a patient with tasimelteon. Tr. 1049:3-1050:19 (Greenblatt).

H. Claim 4 of the ’910 patent is invalid as obvious in light of the prior art.

118. Asserted claim 4 of the ’910 patent depends from claim 3, which depends from claim 2, which depends from claim 1. Claim 1 recites “[a] method of treating a patient for a circadian rhythm disorder wherein the patient is being treated with rifampicin, the method comprising: (A) discontinuing the rifampicin treatment and then (B) treating the patient with tasimelteon, thereby avoiding the use of tasimelteon in combination with rifampicin and also thereby avoiding reduced exposure to tasimelteon caused by induction of CYP3A4 by rifampicin.” JTX-4.41 (40:7-15). Claim 2 specifies that the patient is being treated “for Non-24-Hour Sleep-Wake Disorder.” *Id.* (40:16-17). Claim 3 specifies that the “patient is light perception impaired (LPI).” *Id.* (40:18-19). Claim 4 specifies that “treating

the patient with tasimelteon comprises orally administering to the patient 20 mg of tasimelteon once daily before a target bedtime." *Id.* (40:20-22).

1. The combination of Lankford, Hack, the '244 Publication, and Pandi-Perumal or Hardeland, Hack, the '244 Publication, and Pandi-Perumal renders claim 4 of the '910 patent invalid as obvious.

(a) The Prior Art

(i) Hack, Lankford, the '244 Publication, and Hardeland

119. The teachings of Hack, Lankford, and the '244 Publication are discussed above in Sections II.C.1(a)(i), (ii), and (iv), respectively. The teachings of Hardeland are discussed above in Sections II.C.1(a)(iii) and II.G.1(a)(ii).

(ii) Pandi-Perumal

120. Pandi-Perumal, S.R., et al., "Pharmacotherapy of Insomnia with Ramelteon: Safety, Efficacy and Clinical Applications" ("Pandi-Perumal") was published in 2011 and therefore qualifies as prior art to the '910 patent. JTX-93. Pandi-Perumal is a review article disclosing the use of ramelteon, a melatonin receptor agonist, for the treatment of insomnia. JTX-93.1, 93.2. Further, Pandi-Perumal discloses that potential off-label uses of ramelteon include treating circadian rhythm sleep disorders. JTX-93.1.

121. Pandi-Perumal teaches that ramelteon is a melatonin receptor agonist that specifically acts through the MT1 and MT2 melatonin receptors. JTX-93.1, 93.2. Pandi-Perumal reports that among the reasons that ramelteon was developed

was the desire to have a melatonin receptor agonist with a longer half-life than melatonin (which is approximately 30 minutes). JTX-93.3. Pandi-Perumal discloses that the half-life of circulating ramelteon is 1-2 hours, depending on the dose. *Id*.

122. Pandi-Perumal teaches that ramelteon is metabolized by CYP1A2, CYP2C19, and CYP3A4. JTX-93.4; Tr. 1038:25-1039:13 (Greenblatt). Pandi-Perumal discloses that "[i]n view of the fact that ramelteon is mainly metabolized by CYP1A2 and CYP2C19, drugs that inhibit these enzymes can considerably increase the levels of the agonist." JTX-93.4. More specifically, Pandi-Perumal warns that "ramelteon should not be used in combination with fluvoxamine [or] ciprofloxacin." *Id*. Pandi-Perumal further states, the "CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II" and that "[t]o avoid losses in efficacy, this and other strong upregulators of relevant CYP enzymes should be avoided." *Id*.; Tr. 1051:6-11 (Greenblatt).

(b) The combinations of Lankford, Hack, the '244 Publication, and Pandi-Perumal and Hardeland, Hack, the '244 Publication, and Pandi-Perumal teach or suggest every element of claim 4 of the '910 patent.

123. As explained above, treating blind (i.e., light-perception impaired) Non-24 patients by administering 20 mg tasimelteon before bedtime would have been obvious in view of Lankford, Hack, and the '244 Publication, as well as Hardeland, Hack, and the '244 Publication. And, for the reasons explained herein,

the additional limitation added by claim 4—discontinuing treatment with the CYP3A4 inducer rifampin before administering tasimelteon—would have been obvious in view of Pandi-Perumal and the background knowledge of a skilled artisan. Tr. 1050:20-1052:2 (Greenblatt).

124. Pandi-Perumal discloses that ramelteon is metabolized by CYP1A2, CYP2C19, and CYP3A4. JTX-93.4; Tr. 1038:25-1039:13 (Greenblatt). Pandi-Perumal further discloses that the "CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II." JTX-93.4; Tr. 1051:6-11 (Greenblatt). In view of this, Pandi-Perumal warns that "[t]o avoid losses in efficacy, this and other strong upregulators of relevant CYP enzymes should be avoided." JTX-093.4; Tr. 1051:6-11 (Greenblatt).

125. A skilled artisan intending to administer tasimelteon to a subject already taking rifampin would have been wary given the teachings in Pandi-Perumal, particularly given the background knowledge concerning the similarities between tasimelteon and ramelteon, Tr. 1035:7-18, 1037:5-18, 1040:6-24 (Greenblatt); *see also* DTX-16.3-16.5; JTX-35.1, 35.3, and the very large DDI between ramelteon and rifampin, Tr. 1046:5-1047:5 (Greenblatt); *see also* JTX-93.4; JTX-35.10. Accordingly, a skilled artisan would have found it obvious over Pandi-Perumal in view of the background knowledge in the art to discontinue

treatment with the CYP34 inducer rifampin prior to treating a patient with tasimelteon. Tr. 1047:23-1048:19, 1050:20-1052:2 (Greenblatt).

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CERTIFICATE OF COMPLIANCE

I hereby confirm that this document complies with the type and number limitations set forth in the Court's November 6, 2019 Standing Order and the Stipulation and Order Regarding Post-Trial Briefing (D.I. 305). I certify that this document contains 8,829 words, which were counted using the word count feature in Microsoft Word, in 14-point Times New Roman font. The word count does not include the cover page, tables, or the counsel blocks.

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